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PATENT

Attorney Docket No.: A-63463-1/RFT/RMS/RMK

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of: TOR et al.	Examiner: L. E. Crane
Serial No.: 08/648,270	Group: 1600
Filed: May 15, 1996	Art Unit: 1623
For: SUBSTITUTED PHENANTHROLINES	

CERTIFICATE OF MAILING

I hereby certify that this correspondence, including listed enclosures, is being deposited with the United States Postal Service as First Class Mail in an envelope addressed to: Assistant Commissioner for Patents, Washington, DC 20231 on Mar 23, 2001

Signed: Suzan Lindstrom

DECLARATION UNDER 37 C.F.R. § 1.132 and M.P.E.P. § 716.09

Assistant Commissioner of Patents
Washington, DC 20231

Sir:

I, Thomas J. Meade, do hereby declare as follows:

1. I received a Ph.D. degree in Inorganic Chemistry in 1985 from The Ohio State University. I have been a Senior Research Faculty, Division of Biology and the Beckman Institute, California Institute of Technology for the last 5 years.

2. Attached to this Declaration as Exhibit A is a copy of my curriculum vitae and a list of publications.

3. I am on the Scientific Advisory Board and a consultant for Clinic Micro Sensors, the exclusive licensee of this patent application.

4. I have read and I understand the above-identified patent application, the Preliminary Amendment submitted in response to the Office Action dated July 5, 2000, the exhibits attached to the Preliminary Amendment, and the Office Action mailed January 26, 2001.

5. Based on my understanding, the present invention describes methods of making metal ion complexes comprising 1,10 phenanthroline covalently attached to nucleic acids via acetylene linkages at the 3 and/or 8 positions of the 1.10 phenanthroline moiety. The synthesis of these compounds requires: (1) 1,10 phenanthroline derivatives functionalized at the 3- and/or 8- position; (2) addition of metal ions; (3) a method for covalently attaching nucleic acids to functionalized derivatives of 1,10 phenanthroline; and, (4) the optional incorporation of metal ion complexes comprising 1,10 phenanthroline covalently attached to nucleic acids into oligonucleotides.

6. The Examiner's main point appears to be that the specification does not describe in sufficient detail the method of making transition metal complexes comprising 1,10 phenanthroline covalently attached to nucleic acids via acetylene linkages at the 3 and/or 8 positions. I disagree for the following reasons.

7. First, functionalized derivatives of 1,10 phenanthroline can be made via direct halogenation of commercially available 1,10 phenanthroline monohydrochloride monohydrate. In the specification, one such procedure is described in Example 1. In Example 1, commercially available 1,10 phenanthroline monohydrocholoride monohydrate is treated with bromine to yield two products: 3-bromo-1,10 phenanthroline and 3,8-dibromo-1,10 phenanthroline. Standard purification techniques, such as column chromatography, can be used to separate and purify the two products. In my opinion, the bromination procedure used to make functionalized derivatives of 1,10 phenanthroline is

sufficiently described to allow one of skill in the art to make these compounds without undue experimentation.

8. Second, synthesis of some of the compounds described in the invention requires the addition of metal ions. A typical reaction for adding the transition metal ruthenium to 3,8-dibromo-1,10 phenanthroline is described at page 27, lines 4-13 of the specification. It is my opinion that the procedure described on page 27 may be adapted for the addition of other transition metal ions including copper, cobalt, iron, rhodium, osmium, rhenium, etc. Thus, it is my belief that a person of skill in the art using the procedure outlined on page 27 could readily synthesize derivatives of 1,10 phenanthroline complexed to a number of different metal ions.

9. Third, methods for attaching nucleic acids to the 3-bromo- and 3,8-dibromo-1,10 phenanthroline derivatives are required to form the compounds of the invention. Palladium catalyzed cross coupling reactions are one way to covalently attach nucleic acids to functionalized derivatives of 1,10 phenanthroline. Methods using palladium catalyzed cross coupling reactions to attach nucleic acids to a wide variety of compounds are well known in the art. The references of Robins and Barr, (1983) *J. Org. Chem.*, 48:1854-1862 and Moriarty et al., (1990) *Tetrahedron Letters*, 41:5877-5880, referred to in the preliminary amendment, are examples of methods using palladium catalyzed cross coupling reactions to couple nucleosides to terminal alkynes.

10. It is my opinion, that palladium-mediated cross coupling reaction can be applied to couple nucleosides to aromatic acetylenes derivatives of 1,10 phenanthroline. Sufficient guidance for using the palladium catalyzed cross coupling reaction to couple nucleosides to aromatic acetylene derivatives of 1, 10 phenanthroline is provided in the specification in Scheme II, page 18 of the specification; Scheme IV, page 20 of the

specification; Scheme V, page 20 of the specification and Example 3. Thus, it is my belief that a person of skill in the art using the procedures outlined in the specification could readily synthesize derivatives of 1,10 phenanthroline attached to nucleosides.

11. Finally, methods for synthesizing oligonucleotides are well known in the art. For instance, solid-phase phosphoramidite chemistry may be used to synthesis the metal containing compounds described in the specification. The paper by Hurley and Tor, (1998) J. Am. Chem. Soc., referred to in the Preliminary Amendment, is an example of how the compounds of the present invention may be incorporated into oligonucleotides using solid-phase phosphoramidite chemistry. Furthermore, my lab has recently published a paper where we also incorporate transition metal-containing nucleosides (attached at either the 2' or 5' position of the ribose) into a nucleic acid using solid phase and phosphoramidite chemistry. See Rack et al., J. Amer. Chem. Soc. 122(26):6287-6288 (2000), a copy of which is enclosed as Exhibit A. Thus, it is my opinion that a person of skill in the art using solid-phase phosphoramidite chemistry could make the compounds of the invention without undue experimentation.

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under 18 U.S.C. 1001 and that such willful, false statements may jeopardize the validity/enforceability of the application or any patent issued thereon.

Date: 3-23-01

Thomas J. Meade, Ph.D.

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